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EXAMINER	
LUKTON, DAVID	
ART UNIT	**PAPER NUMBER**
1653	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,477	FOSSA, ANTHONY A.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16 and 18-35* is/are pending in the application.

4a) Of the above claim(s) *1-3,5-12,23-29,32,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,13,14,16,18-22,30,31 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the amendment filed 3/15/04, claims 4 and 13 have been amended to correct minor errors. Claims 1-14, 16 18-35 remain pending. Claims 1-3, 5-12, 23-29, 32, 34, 35 remain withdrawn from consideration. Claims 4, 13, 14, 16, 18-22, 30, 31, 33 are examined in this Office action.

Applicants' arguments filed 3/15/04 have been considered and found not persuasive.

. . .

As before, one or more of the following abbreviations may be used herein:

"**CRF**" = corticotropin releasing factor

"**CRFA**" = corticotropin releasing factor antagonist

"**GHS**" = growth hormone secretagogue

"**GH**" = growth hormone

"**ES-1**" = the first elected specie, i.e., the following:

4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine

"**ES-2**" = the second elected specie, i.e., the following:

2-Amino-N-[1-benzyloxymethyl-2-(2,3a-dimethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo [4,3-c]pyridin-5-yl)-2-oxo-ethyl]-isobutyramide

Claims 4, 13, 14, 16, 18-22, 30, 31, 33 are rejected under the judicially created doctrine of

obviousness-type double patenting as being unpatentable over claim 1 of Carpino (USP 6,107,306) in view of Chen (WO 95/33750).

Carpino discloses (col 1, line 54) that the claimed compounds are effective to treat obesity

Chen discloses (page 8, line 24) use of CRFA's for treating obesity. ["ES-1" is disclosed at p 76, line 27].

Thus, a medical practitioner of ordinary skill would have been motivated to combine the GH of Grandi with the CRFA of Chen for additive effects.

✧

Claims 4, 13, 14, 30, 31, 33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 12 of Chen (USP 5,962,479) in view of Jorgensen (USP 4816439) or Grandi (USP 5268277) or Bengtsson (USP 5,736,515) or Jacobs (USP 5,610,138) or Bennet (USP 5,378,686) or Skakkeb (USP 5,250,514) or Aroonsakul (USP 4,791,099).

Claim 12 of Chen is drawn to a composition for treatment of any of several diseases. At least one of these diseases is disclosed in each of the secondary references, as discussed below in the §103 rejections.

Thus, a medical practitioner of ordinary skill would have been motivated to combine the CRFA of Chen with growth hormone as disclosed in each of the secondary references to achieve additive effects in the treatment of one or more diseases.

✧

Claims 4, 13, 14, 30, 31, 33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 4 of Hamanaka (USP 6,589,947) in view of Grandi (USP 5,268,277).

Claim 4 of Hamanaka is drawn to a pharmaceutical composition which contains the CRFA's to which the instant claims are drawn. Hamanaka discloses (col 5, line 16) that the compounds can be used to treat obesity.

Grandi discloses (col 1, lines 31-35) that growth hormone is effective to treat obesity.

Thus, a medical practitioner of ordinary skill would have been motivated to combine the CRFA of Hamanaka with growth hormone as disclosed in Grandi to achieve additive effects in the treatment of obesity.

✧

Claims 4, 13, 14, 16, 18-22, 30, 31, 33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of Carpino (USP 6,107,306) in view of Hamanaka (USP 6,589,947)

Carpino discloses (col 1, line 54) GHS compounds that are effective to treat obesity. Hamanaka discloses (col 5, line 16) CRFA compounds that can be used to treat obesity.

Thus, a medical practitioner of ordinary skill would have been motivated to combine the GHS compounds of Carpino with the CRFA of Hamanaka for additive effects.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application . See 37 CFR 1.78(d)

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 13, 14, 16, 18-22, 30, 31, 33 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

One may discern two categories of embodiment: (a) those compositions in which growth hormone is present, and (b) those compositions in which growth hormone is not present. This ground of rejection targets the latter.

The instant claims require that the CRFA be one of those that is recited in claim 4. However, it remains to be determined whether any of the compounds (recited in claim 4) are in fact antagonists of corticotropin releasing factor receptors. It is stated p. 69,

lines 23-30 (specification) that one can determine the propensity of compounds to bind to a CRF receptor. No doubt the biochemist of ordinary skill could carry out assays to determine whether or not a compound will bind to a CRF receptor. However, the fact that an assay can be conducted does not mean that any particular result will be obtained. As it happens, where receptor activation and inhibition is concerned, structure/activity relationships are unpredictable. Consider the following:

- Torsello, Antonio (*Endocrinology* **143** (5) 1968, 2002) pertains to growth hormone, and discloses that stimulation of the growth hormone secretagogue receptor does not correlate with capability to stimulate GH secretion.

- McFadyen "Modifications of the cyclic mu receptor selective tetrapeptide Tyr-c[D-Cys-Phe-D-Pen]NH_2 (Et): effects on opioid receptor binding and activation" (*Journal of Peptide Research* (2000 Mar) 55 (3) 255-61) reported on modifications to the title peptide. The reference discloses that potency changes did not always correlate with affinity, suggesting that the conformation required for binding and the conformation required for activation of the opioid receptors are different.

- Keith, "mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain" (*Molecular Pharmacology* **53** (3) 377-84, 1998) discloses that the different effects of individual agonists are not correlated with their potencies for receptor activation and that a variety of clinically important agonists differ significantly in their relative abilities to stimulate the rapid internalization of opioid receptors.

- Xiao (*Biochemistry* **40**, 2860, 2001) has looked at the relationship between cAMP production in cells, and *in vivo* activity. While some degree of correlation was noted, a 1:1 correspondence was absent. As stated on page 2864, col 2, "the results indicated that these functions may be dissociated, mostly likely to additional determinantants of *in vivo* activity...". For example, as conveyed in table 6, Phe'-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 along with decreased *in vivo* insulinotropic activity; by contrast, Acetyl-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 accompanied by an increase in *in vivo* insulinotropic activity. Thus, receptor activation is not necessarily

predictive of *in vivo* activity.

- Lunec, "MSH receptor expression and the relationship to melanogenesis and metastatic activity in B16 melanoma" (*Melanoma Research* (1992 May) 2 (1) 5-12) compared the effects of different pro-opiomelanocortin (POMC) peptides on melanogenesis and metastasis and their relationship to MSH receptor expression in B16F1 melanoma cells. The authors disclose that the relative binding affinities of the different peptides, measured by displacement of [125I]-Nle4-D-Phe7-alpha-MSH, did not closely correlate with the relative potencies in stimulating melanogenesis and metastasis. This suggests that receptor activation and the subsequent biological response is not determined solely by binding affinity

- Keri, Gy ["Structure-activity relationship studies of novel somatostatin analogs with antitumor activity" *Peptide Research* (1993), 6(5), 281-8] discloses (table 4) an example of a peptide which inhibits GH release in vitro, but fails to inhibit GH release in vivo.

- Tolle, V (*Neuroendocrinology* **73** (1) 54-61, 2001) discloses that certain analogs of ghrelin fail to stimulate GH release.

- Rigamonti (*Alcohol* **20** (3) 293-304, 2000) discloses that *gamma*-hydroxybutyric acid and baclofen both fail to stimulate GH release.

- Pinilla L (*Hormone Research* **51** (5) 242-7, 1999) discloses that 8-Br-cGMP was ineffective in eliciting GH release.

- Enright (*Journal of Animal Science* **71** (9) 2395-405, 1993) discloses that thyrotropin releasing hormone was ineffective in eliciting GH release

- Robberecht (*Neuroendocrinology* **56** (4) 550-60, 1992, entitled "Angiotensin II is retained in gonadotrophs of pituitary cell aggregates cultured in serum-free medium but does not mimic the effects of exogenous angiotensins and luteinizing-hormone-releasing hormone on growth hormone release") discloses that LHRH has both inhibitory and stimulatory effects on GH release in cultured pituitary cell aggregates.

The foregoing references support the following conclusions: (a) one cannot "predict"

secretagogue) may be administered.

In addition to asserting that the compounds (contained within the claimed compositions) can promote secretion of GH, or antagonize CRF, applicants have also asserted that the combination of the claimed GHS's and CRFA's are effective to treat various diseases such as osteoporosis, frailty associated with aging, frailty associated with obesity, cardiovascular disease, head related disease, hypertension, tachycardia, and congestive heart failure. It is also asserted that the claimed compositions are effective to accelerate bone fracture repair, attenuate protein catabolic response after surgery, reduce cachexia and protein loss due to chronic illness, accelerate wound healing, and accelerate the recovery of a burn patient or of a patient who has undergone major surgery. Even if applicants could show, at some point in the future, that the claimed compositions are in fact effective to promote secretion of GH, and effective also to antagonize CRF, it would not follow therefrom that even one of the recited diseases could be successfully treated, or that even one of the recited processes (bone fracture repair, wound healing, "recovery") can be achieved. There is no evidence that GHS's in general are effective in this regard, or CRFA's; more importantly there is no evidence that any of the claimed GHS's or CRFA's are effective in this regard.

In response to the foregoing, applicants have made several arguments, beginning with the assertion that all of the claims require growth hormone to be present in the

composition. In reality, however, none of the claims require growth hormone to be present in the composition.

Next, applicants have argued that "evidence of in *vivo activity* is not required for patentability". This particular statement, taken in a vacuum, is not especially meaningful. For example, if an applicant were claiming a refrigeration device or a semiconductor chip or an automobile transmission, it would certainly be true that *in vivo* data would not be required. Further, when an applicant claims a compound, or a mixture of compounds, evidence of *in vivo* activity is generally not required (assuming the term "pharmaceutical" or "therapeutic" is not present in the claim language). However, to the extent that applicants are arguing that a 112, first paragraph rejection applied against a claim to a pharmaceutical composition is necessarily improper as a matter of law, the examiner would disagree. In support of their position, applicants have attributed to the examiner an assertion that the claimed invention lacks patentable utility, and then proceeded to argue that a rejection for lack of utility would be improper. However, the examiner has made no assertion that the claimed compositions lack patentable utility. It is the view of the examiner that traversing rejections that have not been imposed is unproductive. It is suggested that applicants address the issue of enablement, rather than the issue of utility.

Applicants have also cited *In re Wooddy* (331 F2d 636, CCPA, 1964). The

following case has been considered by the examiner: *In re Wooddy and Moore* **141** USPQ 518, 1964). It is true that the first statement in that case is that "law does not require absolute certainty that [a] process will operate in manner claimed...". But it is also true that the Court affirmed the Board's decision, a fact which does not help applicants' position. But in any case, the examiner does not argue that "absolute certainty" is required in the instant case. Rather, the examiner argues that "undue experimentation" would be required to practice the claimed invention.

Next, applicants argue that an applicant need only provide a "reasonable correlation" between the asserted activity and the asserted utility. Again, applicants have imputed to the examiner an assertion that the claimed invention lacks patentable utility, and then proceeded to argue that a rejection for lack of utility would be improper. However, the examiner has made no assertion that the claimed compositions lack patentable utility. In addition, *Cross v Iizuka* is not relevant because it pertained to an interference between to parties; both parties had reason to abstain from arguing lack of enablement. Given that neither of the parties involved had argued lack of enablement, there was no reason for the Court to introduce a new basis for dispute. Courts are in the business of resolving disputes, not creating disputes where none had existed previously. The instant case differs from Cross in that (a) the issue is enablement rather than utility, and (b) there **is** an involved party (i.e., the examiner) who is arguing lack of enablement.

Next, applicants have made an argument that has no scientific basis, i.e., that proof of "correlation" is provided by the fact that other patents have issued, which patents claim the CRFA's and the GHS's. In this particular statement, the sort of "correlation" that may be envisioned by applicants has not been identified. Next, applicants have presented assertions which makes it clear that they believe that a "presumption of validity" equates with "evidence of enablement". Applicants are incorrect on this point. It is certainly true that e.g., Carpino (USP 6,107,306) is a valid patent; the same is true of Chen (USP 6,432,989). But this does not mean that there exists evidence of enablement within these documents. Next, applicants argue the following:

> [The examiner] mistakenly places a burden on the applicant to show that a patent provides evidence of enablement, .i.e., to show that the issued patent is valid. On the contrary, it is the Official Action who has to describe, by clear and convincing evidence, in what way the disclosure of issued U.S. patents, incoporated by reference in the specification of the present application, is not enabling. The clear and convincing evidence standard entails a high burden of proof which clearly has not been met in the instant case.

The first statement is the following: [The examiner] mistakenly places a burden on the applicant to show that a patent provides evidence of enablement, .i.e., to show that the issued patent is valid. Again, applicants are equating "presumption of validity" with "evidence of enablement". To reiterate, the patents of record are valid; but at the

same time, not all of these valid patents provide evidence of enablement. A "presumption of validity" is not the same as "evidence of enablement". The next statement by applicants is the following: "it is the Official Action who has to describe, by clear and convincing evidence, in what way the disclosure of issued U.S. patents, incoporated by reference in the specification of the present application, is not enabling". Applicants are not correct on this point. Neither Carpino (USP 6,107,306) nor Chen (USP 6,432,989) nor any other US Patent is currently under examination. The only document which is subject to examination is serial # 09/834477. The examiner is under no obligation to make an argument (or provide evidence in support thereof) that a US patent is defective or deficient in any way. In fact, it would be improper to do so. To reinforce this point, the examiner now makes clear that he does not now argue, and has not previously argued that Carpino ('306) or Chen ('989) is either defective or deficient. But at the same time, an examiner is not barred from stating the obvious. What is obvious is that there is no evidence of enablement in either of these patents. The examiner does not characterize this lack of evidence as a defect or deficiency insofar as Carpino ('306) and Chen ('989) are concerned. Nevertheless, the fact remains that there does not exist a single published document (or other appropriate evidence) that shows the skilled artisan how to use the compositions claimed in US application 09/834,477.

In the subsequent paragraph (response, page 24) applicants again equate "presumption of validity" with "evidence of enablement". However, these are not the same. Applicants again attempted to impose upon the examiner a standard which no law or statute imposes, i.e., that an examiner must prove invalidity of an issued patent in order to sustain a rejection in a pending patent application. Applicants are simply incorrect as a matter of law; if applicants believe that this is what the law requires, it is suggested that applicants provide some authority for it.

Next, applicants have argued (page 24, response filed 3/15/04) that if it is true that evidence of therapeutic efficacy is lacking, then it must be true that the §103 rejections (below) cannot be valid. However, it is applicants' obligation to overcome all rejections. Further, it is in the interest of "compact prosecution" for an examiner to impose all justifiable rejections concomitantly, even if an applicant believes that two such rejections may be contradictory. Imposing rejections sequentially, rather than concomitantly can sometimes have the effect of unduly prolonging the prosecution. Accordingly, if the §103 and the §112 rejections are going to be imposed at all, it is actually in applicants' interest that they be imposed concomitantly rather than sequentially.

✧

The following is a quotation of 35 USC. §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 4, 13, 14, 16, 18-22, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Carpino (USP 6,107,306) in view of Chen (USP 6,432,989).

As indicated previously, Carpino discloses treatment of sleep disorders using GHS's; also disclosed (col 64, line 12) is "ES-2". Carpino does not suggest combining a GHS with a CRFA.

Chen discloses treatment of sleep disorders; also disclosed (col 27, line 36) is "ES-1". Chen does not suggest combining a GHS with a CRFA..

In response to the foregoing, applicants have argued that neither of the references qualifies

as prior art. Applicants' attorney has further stated that, at the time of the invention, the instant application was subject to an obligation of assignment to Pfizer. It is further stated that Carpino ('306) and Chen (USP '989) are both currently assigned to Pfizer. What is absent from the statement by applicants' attorney is that at the time of the (instantly claimed) invention, Carpino ('306) and Chen (USP '989) were (at that time) subject to an obligation of assignment to Pfizer. If this was the case, it is suggested that applicants' attorney make a statement to this effect.

Thus, technically, applicants' representative has not fully disqualified the references as prior art. In addition, the other arguments (as to the merits of the rejection) are found to be unpersuasive. Applicants have argued that because neither reference taken by itself qualifies as a proper rejection under 35 USC §102, the rejection must be improper. However, it is always the case that when a rejection is imposed under 35 USC §103, there is a deficiency in at least one of the cited references. Thus, a deficiency in a reference is not, in and of itself, a sufficient reason to conclude that a §103 rejection is improper. In the instant case, a pharmacologist of ordinary skill would have expected additive effects in combining the two agents. As is known to the pharmacologist of ordinary skill, increasing the dosage of a drug generally increases the pharmacological effect, at least up to a saturation point. (Beyond that point there is no additional beneficial effect to increasing the dosage). But at dosages below the "saturation point", the pharmacologist of

ordinary skill would expect an "additive effect" for a single drug (i.e., increasing the dosage). Similarly, one would expect that if drug "X" is effective to treat a given disorder, and drug "Y" is effective to treat the same disorder, then for dosages below the "saturation point" of drug "X" and drug "Y", a combination of drug "X" and drug "Y" will provide a greater therapeutic effect than would be the case for drug "X" alone (or drug "Y" alone). Thus, the medical practitioner endeavoring to treat sleep disorders would have expected a greater therapeutic effect when the GHS (of Carpino) is combined with the CRFA (of Chen) than would have been the case if either agent were administered separately.

✧

Claims 4, 13, 14, 16, 18-22, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Carpino (USP 6,107,306) in view of Chen (USP 5,962,479).

As indicated previously, Carpino discloses treatment of Alzheimer's Disease using GHS's; also disclosed (col 64, line 12) is "ES-2". Carpino does not suggest combining a GHS with a CRFA.

Chen discloses treatment of Alzheimer's Disease; also disclosed (col 55, line 34) is "ES-1". Chen does not suggest combining a GHS with a CRFA..

In response to the foregoing, applicants have argued that Carpino ('306) is not available as prior art. As indicated above, what is absent from the statement by applicants' attorney is that at the time of the (instantly claimed) invention, Carpino ('306) was (at that time)

subject to an obligation of assignment to Pfizer.

✧

Claims 4, 13, 14, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Jorgensen (USP 4,816,439) in view of Chen (WO 95/33750).

Jorgensen discloses the use of GH for treating patients afflicted with chemical dependencies and addictions. Jorgensen does not suggest combining GH with a CRFA to achieve additive effects.

Chen discloses (page 7, line 27) use of CRFA's for treating chemical dependencies and addictions. ["ES-1" is disclosed at p 76, line 27]

Thus, a medical practitioner of ordinary skill would have been motivated to combine the GH of Jorgensen with the CRFA of Chen for additive effects.

✧

Claims 4, 13, 14, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Grandi (USP 5,268,277) in view of Chen (WO 95/33750).

Grandi discloses (col 1, lines 31-35) that growth hormone is effective to treat obesity Grandi does not suggest combining GH with a CRFA to achieve additive effects.

Chen discloses (page 8, line 24) use of CRFA's for treating obesity. ["ES-1" is disclosed at p 76, line 27]

Thus, a medical practitioner of ordinary skill would have been motivated to combine the

GH of Grandi with the CRFA of Chen for additive effects.

✧

Claims 4, 13, 14, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Bengtsson (USP 5736515) in view of Chen (WO 95/33750)

Bengtsson discloses (col 2, lines 1-11) that growth hormone is effective to treat depression, neurodegenerative disorders, ischemia and dementia. Bengtsson does not suggest combining GH with a CRFA to achieve additive effects.

Chen discloses (pages 7-8) use of CRFA's for treating various diseases, including depression, neurodegenerative disorders, ischemia and dementia. ["ES-1" is disclosed at p 76, line 27].

Thus, a medical practitioner of ordinary skill would have been motivated to combine the GH of Bengtsson with the CRFA of Chen for additive effects.

✧

Claims 4, 13, 14, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Jacobs (USP 5,610,138) in view of Chen (WO 95/33750).

Jacobs discloses that growth hormone is effective to treat infertility. Jacobs does not suggest combining GH with a CRFA to achieve additive effects.

Chen discloses (page 8, line 24) use of CRFA's for treating infertility. ["ES-1" is disclosed at p 76, line 27].

Thus, a medical practitioner of ordinary skill would have been motivated to combine the GH of Jacobs with the CRFA of Chen for additive effects.

✧

Claims 4, 13, 14, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Bennet (USP 5378686) in view of Chen (WO 95/33750)

Bennet discloses that growth hormone is effective to treat fibromyalgia. Bennet does not suggest combining GH with a CRFA to achieve additive effects.

Chen discloses (page 7, line 20) use of CRFA's for treating fibromyalgia. ["ES-1" is disclosed at p 76, line 27].

Thus, a medical practitioner of ordinary skill would have been motivated to combine the GH of Bennet with the CRFA of Chen for additive effects.

✧

Claims 4, 13, 14, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Skakkeb (USP 5,250,514) in view of Chen (WO 95/33750).

Skakkeb discloses that growth hormone is effective to treat infertility. Skakkeb does not suggest combining GH with a CRFA to achieve additive effects.

Chen discloses (page 8, line 15) use of CRFA's for treating infertility. ["ES-1" is disclosed at p 76, line 27].

Thus, a medical practitioner of ordinary skill would have been motivated to combine the

GH of Skakkeb with the CRFA of Chen for additive effects.

✧

Claims 4, 13, 14, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Aroonsakul (USP 4,791,099) in view of Chen (WO 95/33750).

Aroonsakul discloses (e.g., col 6, line 16+) that growth hormone in combination with an androgen is effective to treat various neurological diseases such as Parkinson's and Alzheimer's. Aroonsakul does not suggest combining GH with a CRFA to achieve additive effects.

Chen discloses (pages 7-8) use of CRFA's for treating various diseases, including Parkinson's and Alzheimer's Diseases. ["ES-1" is disclosed at p 76, line 27].

Thus, a medical practitioner of ordinary skill would have been motivated to combine the GH of Aroonsakul with the CRFA of Chen for additive effects.

✧

Claims 4, 13, 14, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Jorgensen (USP 4816439) in view of Chen (WO 95/33750) further in view of Rivier (*Endocrinology* **114**, 2409-11 1984).

Jorgensen discloses the use of GH for treating patients afflicted with chemical dependencies and addictions. Jorgensen does not suggest combining GH with a CRFA to achieve additive effects.

Chen discloses (page 7, line 27) use of CRFA's for treating chemical dependencies and addictions. ["ES-1" is disclosed at p 76, line 27].

Rivier discloses that CRF inhibits GH secretion. Rivier does not suggest combining GH with a CRFA to achieve additive effects.

Thus, Chen discloses the desirability of antagonizing CRF in endeavoring to treat a disease or disorder, and Rivier discloses that CRF inhibits GH secretion. One (of ordinary skill) would therefore reason that the adverse effect of CRF is due, at least in part, to suppression of GH. Accordingly, the medical practitioner of ordinary skill would have been motivated to combine a CRFA with GH in order to mitigate the adverse effects of excess CRF.

✧

Claims 4, 13, 14, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Grandi (USP 5268277) in view of Chen (WO 95/33750) further in view of Rivier (*Endocrinology* **114**, 2409-11 1984).

Grandi discloses (col 1, lines 31-35) that growth hormone is effective to treat obesity Grandi does not suggest combining GH with a CRFA to achieve additive effects.

Chen discloses (page 8, line 24) use of CRFA's for treating obesity. ["ES-1" is disclosed at p 76, line 27]

Rivier discloses that CRF inhibits GH secretion. Rivier does not suggest combining GH with a CRFA to achieve additive effects.

Thus, Chen discloses the desirability of antagonizing CRF in endeavoring to treat a disease or disorder, and Rivier discloses that CRF inhibits GH secretion. One (of ordinary skill) would therefore reason that the adverse effect of CRF is due, at least in part, to suppression of GH. Accordingly, the medical practitioner of ordinary skill would have been motivated to combine a CRFA with GH in order to mitigate the adverse effects of excess CRF.

✧

Claims 4, 13, 14, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Bengtsson (USP 5736515) in view of Chen (WO 95/33750) further in view of Rivier (*Endocrinology* **114**, 2409-11 1984).

Bengtsson discloses (col 2, lines 1-11) that growth hormone is effective to treat depression, neurodegenerative disorders, ischemia and dementia. Bengtsson does not suggest combining GH with a CRFA to achieve additive effects.

Chen discloses (pages 7-8) use of CRFA's for treating various diseases, including depression, neurodegenerative disorders, ischemia and dementia. ["ES-1" is disclosed at p 76, line 27].

Thus, Chen discloses the desirability of antagonizing CRF in endeavoring to treat a disease or disorder, Rivier discloses that CRF inhibits GH secretion. One (of ordinary skill) would therefore reason that the adverse effect of CRF is due, at least in part, to suppression of GH. Accordingly, the medical practitioner of ordinary skill would have been motivated

to combine a CRFA with GH in order to mitigate the adverse effects of excess CRF.

✧

Claims 4, 13, 14, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Jacobs (USP 5,610,138) in view of Chen (WO 95/33750) further in view of Rivier (*Endocrinology* **114**, 2409-11 1984).

Jacobs discloses that growth hormone is effective to treat infertility. Jacobs does not suggest combining GH with a CRFA to achieve additive effects.

Chen discloses (page 8, line 24) use of CRFA's for treating infertility. ["ES-1" is disclosed at p 76, line 27].

Thus, Chen discloses the desirability of antagonizing CRF in endeavoring to treat a disease or disorder, and Rivier discloses that CRF inhibits GH secretion. One (of ordinary skill) would therefore reason that the adverse effect of CRF is due, at least in part, to suppression of GH. Accordingly, the medical practitioner of ordinary skill would have been motivated to combine a CRFA with GH in order to mitigate the adverse effects of excess CRF.

✧

Claims 4, 13, 14, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Bennet (USP 5378686) in view of Chen (WO 95/33750) further in view of Rivier (*Endocrinology* **114**, 2409-11 1984).

Bennet discloses that growth hormone is effective to treat fibromyalgia. Bennet does not

suggest combining GH with a CRFA to achieve additive effects.

Chen discloses (page 7, line 20) use of CRFA's for treating fibromyalgia. ["ES-1" is disclosed at p 76, line 27].

Thus, Chen discloses the desirability of antagonizing CRF in endeavoring to treat a disease or disorder, and Rivier discloses that CRF inhibits GH secretion. One (of ordinary skill) would therefore reason that the adverse effect of CRF is due, at least in part, to suppression of GH. Accordingly, the medical practitioner of ordinary skill would have been motivated to combine a CRFA with GH in order to mitigate the adverse effects of excess CRF.

✧

Claims 4, 13, 14, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Skakkeb (USP 5,250,514) in view of Chen (WO 95/33750) further in view of Rivier (*Endocrinology* **114**, 2409-11 1984).

Skakkeb discloses that growth hormone is effective to treat infertility. Skakkeb does not suggest combining GH with a CRFA to achieve additive effects.

Chen discloses (page 8, line 15) use of CRFA's for treating infertility. ["ES-1" is disclosed at p 76, line 27].

Thus, Chen discloses the desirability of antagonizing CRF in endeavoring to treat a disease or disorder, and Rivier discloses that CRF inhibits GH secretion. One (of ordinary skill) would therefore reason that the adverse effect of CRF is due, at least in part, to suppression

of GH. Accordingly, the medical practitioner of ordinary skill would have been motivated to combine a CRFA with GH in order to mitigate the adverse effects of excess CRF.

✧

Claims 4, 13, 14, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Aroonsakul (USP 4,791,099) in view of Chen (WO 95/33750) further in view of Rivier (*Endocrinology* **114**, 2409-11 1984).

Aroonsakul discloses (e.g., col 6, line 16+) that growth hormone in combination with an androgen is effective to treat various neurological diseases such as Parkinson's and Alzheimer's. Aroonsakul does not suggest combining GH with a CRFA to achieve additive effects.

Chen discloses (pages 7-8) use of CRFA's for treating various diseases, including Parkinson's and Alzheimer's Diseases. ["ES-1" is disclosed at p 76, line 27].

Thus, Chen discloses the desirability of antagonizing CRF in endeavoring to treat a disease or disorder, and Rivier discloses that CRF inhibits GH secretion. One (of ordinary skill) would therefore reason that the adverse effect of CRF is due, at least in part, to suppression of GH. Accordingly, the medical practitioner of ordinary skill would have been motivated to combine a CRFA with GH in order to mitigate the adverse effects of excess CRF.

✧

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

D. Lukton

DAVID LUKTON
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